

We claim:

1. An isolated human monoclonal antibody which specifically binds to HER2/neu and inhibits growth of cells expressing HER2/neu, produced from a transgenic non-  
5 human animal.
2. The human antibody of claim 1, wherein the antibody binds to human HER2/neu with an equilibrium association constant ( $K_a$ ) of at least  $10^8 \text{ M}^{-1}$ .
- 10 3. The human antibody of claim 1, wherein the antibody binds to human HER2/neu with an equilibrium association constant ( $K_a$ ) of at least  $10^9 \text{ M}^{-1}$ .
4. The human antibody of claim 1, wherein the antibody inhibits tumor cell growth by at least about 40%.
- 15 5. The human antibody of claim 1, wherein the antibody inhibits tumor cell growth by at least about 60%.
6. The human antibody of claim 1, wherein the antibody does not bind to EGFR.
- 20 7. The human antibody of claim 1, wherein the antibody heavy chain is an IgG1 or IgG3 heavy chain.
8. An isolated human monoclonal antibody encoded by human IgG heavy chain  
25 and human kappa light chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID NO:1 and SEQ ID NO:3, respectively, and conservative sequence modifications thereof.
9. An isolated human monoclonal antibody having IgG heavy chain and kappa light  
30 chain variable regions which comprise the amino acid sequences shown in SEQ ID NO:2 and SEQ ID NO:4, respectively, and conservative sequence modifications thereof.

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10. An isolated human monoclonal antibody encoded by human IgG heavy chain and human kappa light chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID NO:5 and SEQ ID NO:7, respectively, and  
5 conservative sequence modifications thereof.

11. An isolated human monoclonal antibody having IgG heavy chain and kappa light chain variable regions which comprise the amino acid sequences shown in SEQ ID NO:6 and SEQ ID NO:8, respectively, and conservative sequence modifications thereof.

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12. An isolated human monoclonal antibody encoded by human IgG heavy chain and human kappa light chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID NO:9 and SEQ ID NO:11, respectively, and conservative sequence modifications thereof.

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13. An isolated human monoclonal antibody having IgG heavy chain and kappa light chain variable regions which comprise the amino acid sequences shown in SEQ ID NO:10 and SEQ ID NO:12, respectively, and conservative sequence modifications thereof.

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14. The human antibody of claim 1, wherein the antibody has at least one of the characteristics selected from the group consisting of:

- a) a binding affinity constant of at least about  $10^8 \text{ M}^{-1}$ ;
- b) an association constant ( $K_{\text{assoc}}$ ) of at least about  $10^4$ ; and
- 25 c) the ability to opsonize a cell expressing HER2/neu; or
- d) the ability to mediate cytolysis of a cell expressing HER2/neu in the presence of human effector cells at a concentration of about  $10 \mu\text{g/ml}$  or less *in vitro*.

15. The human antibody of claim 1, wherein the cell expressing HER2/neu is a  
30 tumor cell.

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16. The human antibody of claim 15, wherein the cell expressing HER2/neu is selected from the group consisting of an adenocarcinoma cell, e.g. salivary gland, stomach and kidney, a mammary gland carcinoma cell, a lung carcinoma cell, a squamous cell carcinoma cell, and an ovarian cancer cell.

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17. The human antibody of claim 1, produced by a hybridoma which includes a B cell obtained from a transgenic non-human animal having a genome comprising a human heavy chain transgene and a human light chain transgene fused to an immortalized cell.

10 18. An isolated human monoclonal antibody produced by a hybridoma selected from the group consisting of 3.F2, 2.E8, 1.D2, 1.B10 and 3.B4.

19. An isolated human monoclonal antibody which specifically binds to HER2/neu and mediates cytolysis of cells expressing HER2/neu in the presence of human effector  
15 cells, wherein the antibody is produced from a transgenic non-human animal.

20. The isolated human antibody of claim 8, or an antigen binding portion thereof, which is capable of mediating cytolysis of cells expressing HER2/neu by human effector cells at an  $IC_{50}$  of  $1 \times 10^{-7}$  M or less *in vitro*.

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21. A hybridoma comprising a B cell obtained from a transgenic non-human animal having a genome comprising a human heavy chain transgene and a light chain transgene, fused to an immortalized cell, wherein the hybridoma produces a human monoclonal antibody that specifically binds to HER2/neu.

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22. The hybridoma of claim 21 which produces a human monoclonal antibody encoded by human IgG heavy chain and human kappa light chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID NO:1 and SEQ ID NO:3, respectively, and conservative sequence modifications thereof.

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23. The hybridoma of claim 21 which produces a human monoclonal having IgG heavy chain and kappa light chain variable regions which comprise the amino acid sequences shown in SEQ ID NO:2 and SEQ ID NO:4, respectively, and conservative sequence modifications thereof.

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24. The hybridoma of claim 21 which produces a human monoclonal antibody encoded by human IgG heavy chain and human kappa light chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID NO:5 and SEQ ID NO:7, respectively, and conservative sequence modifications thereof.

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25. The hybridoma of claim 21 which produces a human monoclonal having IgG heavy chain and kappa light chain variable regions which comprise the amino acid sequences shown in SEQ ID NO:6 and SEQ ID NO:8, respectively, and conservative sequence modifications thereof.

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26. The hybridoma of claim 21 which produces a human monoclonal antibody encoded by human IgG heavy chain and human kappa light chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID NO:9 and SEQ ID NO:11, respectively, and conservative sequence modifications thereof.

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27. The hybridoma of claim 21 which produces a human monoclonal antibody having IgG heavy chain and kappa light chain variable regions which comprise the amino acid sequences shown in SEQ ID NO:10 and SEQ ID NO:12, respectively, and conservative sequence modifications thereof.

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28. The hybridoma of claim 21, selected from the group consisting of 3.F2, 2.E8, 1.D2., 1.B10, and 3.B4.

29. A transgenic non-human animal which expresses a human monoclonal antibody  
30 that specifically binds to HER2/neu, wherein the transgenic non-human animal has a genome comprising a human heavy chain transgene and a human light chain transgene.

30. A method of producing a human monoclonal antibody that specifically binds to HER2/neu, comprising:
- immunizing a transgenic non-human animal having a genome comprising a human heavy chain transgene and a human light chain transgene with HER2/neu or a cell  
5 expressing HER2/neu, such that antibodies are produced by B cells of the animal;  
isolating B cells of the animal; and  
fusing the B cells with myeloma cells to form immortal, hybridoma cells that secrete human monoclonal antibodies specific for HER2/neu.
- 10 31. A bispecific molecule comprising a first binding specificity which is a human monoclonal antibody, or an antigen binding portion thereof, that specifically binds to HER2/neu, and a second binding specificity for an Fc receptor.
32. The bispecific molecule of claim 31, wherein the Fc receptor is a human Fc $\gamma$ RI  
15 or a human Fc $\alpha$  receptor.
33. The bispecific molecule of claim 31, which binds to the Fc receptor at a site which is distinct from the immunoglobulin binding site of the receptor.
- 20 34. The bispecific molecule of claim 31, wherein the second binding specificity which binds to an Fc receptor is a human monoclonal antibody or an antigen binding portion thereof.
35. The bispecific molecule of claim 31 which is a single chain or Fab' fusion  
25 protein.
36. A multispecific molecule comprising a first binding specificity which is a human monoclonal antibody, or an antigen binding portion thereof, that specifically binds to HER2/neu, a second binding specificity for an Fc receptor, and a third binding specificity  
30 for a tumor antigen other than HER2/neu.

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37. The multispecific molecule of claim 36, wherein the third binding specificity is EGF.

38. A composition comprising an isolated human monoclonal antibody which  
5 specifically binds to HER2/neu, and a pharmaceutically acceptable carrier, wherein the antibody is produced from a transgenic non-human animal.

39. The composition of claim 38 comprising a combination of two or more isolated  
10 human antibodies which specifically bind to HER2/neu, wherein each of said antibodies binds to a distinct epitope of HER2/neu.

40. The composition of claim 38 further comprising a chemotherapeutic agent.

41. A method of inhibiting growth of a cell expressing HER2/neu, comprising  
15 contacting a cell expressing HER2/neu with an isolated human monoclonal antibody that specifically binds to HER2/neu, such that the growth of the cell is inhibited, wherein the antibody is produced from a transgenic non-human animal.

42. A method of inducing cytolysis of a cell expressing HER2/neu, comprising  
20 contacting a cell expressing HER2/neu with an isolated human monoclonal antibody that specifically binds to HER2/neu, in the presence of an effector cell, such that cytolysis of the cell expressing HER2/neu occurs, wherein the antibody is produced from a transgenic non-human animal.

25 43. A method of treating or preventing a disease characterized by aberrant expression of HER2/neu, comprising administering to a subject an isolated human monoclonal antibody that specifically binds to HER2/neu in an amount effective to treat or prevent the HER2/neu-mediated disease, wherein the antibody is produced from a transgenic non-human animal.

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44. The method of any of claims 41-43, wherein the human monoclonal antibody is conjugated to a binding specificity for a Fc receptor.

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45. The method of claim 44, wherein the human monoclonal antibody is conjugated to a cytotoxin.

46. The method of claim 44, wherein the disease is a cancer.

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47. The method of claim 46, wherein the cancer is selected from the group consisting of an adenocarcinoma, *e.g.* salivary gland, stomach and kidney, mammary gland carcinoma, lung carcinoma, squamous cell carcinoma, and ovarian cancer.

10 48. A method for detecting the presence of HER2/neu antigen, or a cell expressing HER2/neu, in a sample comprising:  
contacting the sample, and a control sample, with a human monoclonal antibody which specifically binds to HER2/neu, wherein the antibody is produced from a transgenic non-human animal, under conditions that allow for formation of a complex  
15 between the antibody or portion thereof and HER2/neu; and  
detecting the formation of a complex,  
wherein a difference complex formation between the sample compared to the control sample is indicative the presence of HER2/neu in the sample.

20 49. A nucleic acid comprising a nucleotide sequence encoding a variable region of a human monoclonal antibody that specifically binds to HER2/neu, wherein the nucleotide sequence is selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9 and SEQ ID NO:11.

25 50. An immunotoxin comprising a human monoclonal antibody which specifically binds to HER2/neu linked to a cytotoxic agent, wherein the antibody is produced from a transgenic non-human animal.

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